

Appl. No. 10/003,621
Amdt. dated March 15, 2004
Reply to Office Action of December 15, 2003

PATENT

Amendments to the Drawings:

The attached sheets of drawings include changes to Figs. 1 and 2. These sheets, which include Figs. 1 and 2, replace the original sheets including Figs. 1 and 2.

Attachment: Replacement Sheets

REMARKS

I. **Status of the Claims**

Claims 17-22 are currently pending. Upon entry of this amendment, claims 17-20 are amended without prejudice or disclaimer. Applicants reserve the right to reintroduce the unamended claims in this or another application. These claims are amended to improve the clarity of the claims. New claims 23-28 are also introduced upon entry of this amendment. Claims 17-28 are thus pending following entry of this amendment.

The new claims are supported throughout the specification, including, for example, the following sections:

Claim 23:	page 24, lines 1-2
Claims 24-26:	page 7, third full paragraph to page 8, first partial paragraph
Claims 27-28:	paragraph bridging pages 10 and 11

II. **Objections to the Specification and Specification Amendments**

The trademarks identified in the Office Action have been capitalized as requested. It is submitted that the specification already includes a generic description of the materials that are referred to by trademarks (e.g., the various cation exchange materials listed on page 7 are indicated as being sulfopropyl- or carboxymethyl-group conjugated cation exchangers).

The title has been amended to reflect more accurately the subject matter of the currently claimed invention.

The other amendments to the specification are to insert appropriate section headings and to move the description of the figures so the specification is consistent with the provisions of MPEP 601.

None of these amendments introduce new matter.

III. **Priority**

A copy of the priority application will be submitted separately.

IV. Drawings

A set of formal drawings are attached to this paper. These figures differ from the originals simply in that they bring the figures into conformity with the formal requirements of 37 C.F.R. 1.84, specifically by providing cleaner versions with improved figure numbering.

V. Claim Rejections under 35 U.S.C. §112, Second Paragraph

Claim 17 has been amended to spell-out the acronym vWF as requested. Claim 18 has been amended to amend the phrase "particularly free" to "free" as suggested.

VI. Claim Rejections under 35 U.S.C. §103

Claims 17-22 are rejected under 35 U.S.C. §103 as obvious over Arrighi et al. (EP 600 480; "Arrighi") in view of Fischer et al. [EP 705 846 (equivalent English version is US Patent No. 5,869,617); "Fischer"]. Arrighi is said to discuss a method for purifying factor VIII/vWF complexes that includes cation exchange chromatography. It is concluded that the purified factor VIII/vWF complex that results from this process is indistinguishable from the factor VIII/vWF complexes that are currently claimed. Although the Office Action acknowledges that Arrighi lacks any discussion of pharmaceutical compositions, Fischer is said to discuss methods and pharmaceutical compositions relating to high and low molecular weight forms of vWF and thus to provide the motivation to formulate the complexes discussed in Arrighi to obtain the claimed preparations. It is thus concluded that the claimed complexes and compositions are obvious in view of the combined disclosures of these two references. For the reasons that follow, Applicants disagree.

The Office appears to take the position that the factor VIII/vWF complexes obtained in Arrighi must necessarily have the characteristics of the complexes that are currently claimed because both Arrighi and the current application discuss methods for obtaining such complexes using cation exchange chromatography. But the cation exchange purification approach described in the application differs in significant respects from that discussed in Arrighi, and thus yields compositions containing factor VIII/vWF complexes that differ from those discussed in Arrighi.

This is illustrated, for instance, with respect to the factor VIII/vWF complexes that are described in claim 24. The complexes of this claim are obtained by eluting factor VIII/vWF complexes that are adsorbed to a cation exchanger by a *step-wise* elution process. During this process, complexes containing low-molecular weight vWF complexes are preferentially eluted in one step and complexes containing high-molecular weight vWF complexes are eluted in a separate step. In this way, complexes containing low-molecular weight vWF multimers can be selectively separated from complexes containing high-molecular weight vWF multimers. As noted in the specification, the ability to separate these differing complexes can be important because complexes enriched in high-molecular weight vWF multimers are preferred in certain blood treatments as compared to complexes that contain a significant amount of low-molecular weight vWF multimers (see, e.g., last paragraph on page 3).

Arrighi, in contrast, discusses a very complicated process of purifying factor VIII/vWF complexes, in which one step in the overall process is a cation exchange step. Unlike the *step-wise* elution process described in the application, however, factor VIII/vWF complexes in the Arrighi cation exchange process are eluted in a *single* step. More specifically, Arrighi discusses a cation exchange process in which non-absorbed or weakly bound proteins (there is no indication in Arrighi that this includes any form of a factor VIII/vWF-complex) are initially eluted with a TC buffer (see, col. 4, lines 15-17; and col. 3, lines 4-7). "The FVIII:C-FvW complex" is subsequently eluted with TE buffer (see, col. 4, lines 17-20). Because the Arrighi method involves eluting all types of factor VIII/vWF-complexes from the cation exchanger in a *single* step, the resulting eluant would be expected to contain factor VIII/vWF-complexes that contain low-molecular weight vWF multimers in addition to complexes that contain high-molecular weight vWF multimers. So although at first glance it might appear that the two cation exchange methods are the same, they are upon closer examination significantly different.

It is also noted that Arrighi lacks any discussion that would suggest purification conditions that are suitable for addressing the difficulties associated with obtaining the presently claimed complexes. For instance, a major difficulty in the purification of a protein/protein complex such as the factor VIII/vWF-complex is to identify appropriate elution conditions that prevent the components of the complex (which are not covalently bound but associated by

electrostatic forces) from disassociating from one another (e.g., factor VIII disassociating from vWF). This difficulty is further compounded if the goal is to obtain factor VIII/vWF-complexes that contain high molecular weight vWF multimers, because the elution conditions must also be tailored such that high molecular weight vWF multimers rather than low molecular weight vWF multimers are obtained. There is no discussion in Arrighi regarding any of these issues whatsoever.

The foregoing differences between the complexes discussed in Arrighi and those that are currently claimed are also highlighted with respect to claim 17. This claim currently states that the claimed factor VIII/vWF complexes are free from low-molecular weight vWF multimers. For the reasons just articulated, however, the factor VIII/vWF complexes obtained by the Arrighi methods would be expected to contain significant amounts of low-molecular weight vWF multimers.

The factor VIII/vWF complexes recited in claim 19 are also distinct from those discussed in Arrighi. The complexes in the Arrighi methods, for example, are at best said to have a specific vWF activity of 30-50 IU/mg of protein (see column 2, lines 12-13 and column 4, line 20). The complexes described in claim 19, however, are characterized as having a specific vWF activity of at least 66 U/mg of protein. This is at least a 32% improvement in activity as compared to the Arrighi complexes. The Office Action attempts to dismiss this difference by pointing to one example in the specification that refers to a process in which the specific Factor VIII activity is 12 IU/mg of protein and to a section from Arrighi (lines 43-47 of column 5) that refers to a purified composition having a specific Factor VIII activity of 8-15 IU/mg of protein. The Office Action thus concludes that Arrighi "achieved a purity that is equal or higher than the claimed invention."

There are several problems with this analysis. First, the analysis focuses on the lowest activity levels discussed in the application but ignores the results described on pages 23-24 of the specification and statements elsewhere (e.g., first full paragraph on page 11) that describe complexes in which the specific activity of Factor VIII was 477-500 IU/mg and the specific activity of vWF was 66-83 U/mg. These activities are significantly above those discussed in Arrighi. Furthermore, the section the Office Action points to is almost certainly a

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typographical error. This section is likely intended to refer to the activity level of FVII rather than FVIII since the cited discussion falls within a section entitled "Factor VII Purification" and all earlier references in this section refer to FVII instead of FVIII. Regardless, the current application describes complexes in which both the Factor VIII and vWF specific activities are significantly above any activity levels disclosed in Arrighi.

Finally, it is noted that Fischer does not compensate for any of the foregoing deficiencies in Arrighi. Fischer focuses on methods for purifying vWF rather than factor VIII/vWF complexes, and thus is of limited relevance to the currently claimed invention. Consequently, even when the disclosure of Arrighi and Fischer are combined, these references fail to teach each and every element of the currently pending claims as required to establish a *prima facie* case of obviousness. It is accordingly requested that this rejection be withdrawn.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 303-571-4000.

Respectfully submitted,


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